SCIENTIFIC ABSTRACT

A Phase I Study of Vaccination with Autologous, Irradiated Melanoma Cells Engineered to Secrete Human Granulocyte-Macrophage Colony Stimulating Factor

This clinical trial for patients with metastatic melanoma will investigate the use as therapeutic vaccines of autologous, irradiated melanoma cells engineered by retroviral mediated gene transfer to secrete human granulocyte-macrophage colony stimulating factor (GM-CSF). A total of 16-25 patients will be treated at three different dose levels of vaccine. Each patient will receive inoculations of $1x10^7$ autologous melanoma cells (secreting 40-1000 ng of GM-CSF/10^6 cells/24 hours) subcutaneously and intradermally. The interval between vaccinations will be varied from every month to every two weeks to weekly for a total duration of three months. This design will test the effects of increasing both the frequency of vaccination and the total number of cells and GM-CSF administered.

The proposed study is based on pre-clinical experiments in murine tumor model systems which indicated that injection of irradiated tumor cells engineered to secrete murine granulocyte-macrophage colony stimulating factor generated potent, specific, and long lasting anti-tumor immunity. Efficacy of irradiated, GM-CSF expressing cells could be demonstrated in models of melanoma, renal cell carcinoma, fibrosarcoma, lung carcinoma, colon carcinoma, neuroblastoma, bladder carcinoma, and prostate carcinoma.

The MFG-S replication defective retroviral vector provides efficient transfer and expression of the gene encoding human granulocyte-macrophage colony stimulating factor in primary short term melanoma explants. As no selection for transduced cells is required, antigenic heterogeneity within the vaccinating inoculum is relatively preserved. The vaccinating cells are lethally irradiated with 15,000 rads (which does not interfere with their GM-CSF production) to provide safeguards against both the injection of tumor cells potentially rendered more virulent by in vitro manipulation or insertional mutagenesis, and the autonomous growth of nonneoplastic cells induced by autocrine synthesis of their own growth factors.

The overall goals of the proposed phase I study are:

1. To evaluate the safety of clinical administration of autologous, irradiated melanoma cells engineered, by retroviral mediated gene transfer, to secrete human granulocyte-macrophage colony stimulating factor.

2. To determine, if possible, the dose limiting toxicity (DLT) and maximum tolerated dose (MTD) of autologous, irradiated melanoma cells engineered to express GM-CSF.

3. To describe and quantify any local or systemic immune response stimulated by vaccination with autologous, irradiated GM-CSF expressing cells.